Multiple Sclerosis: from Neurobiology to Therapy

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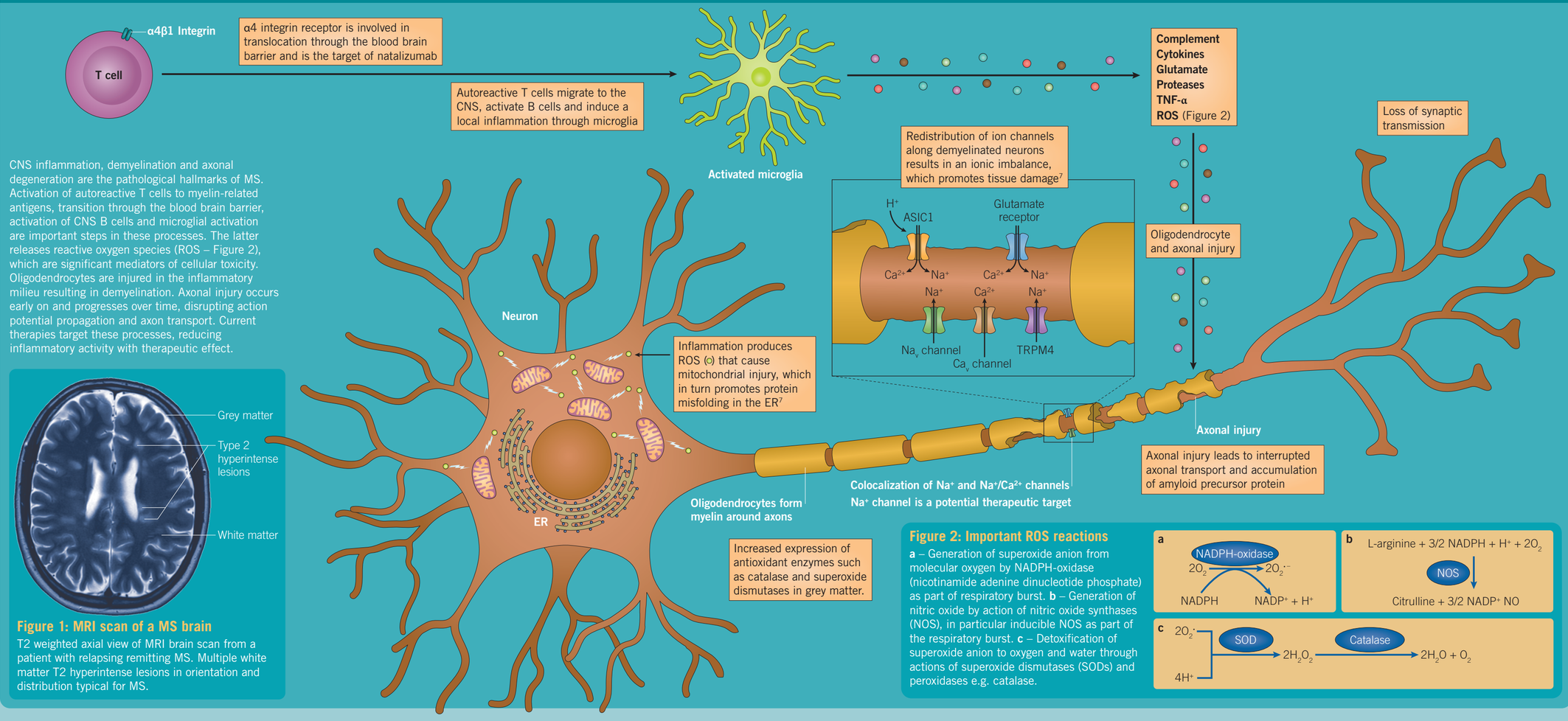
Multiple sclerosis (MS) is an autoimmune, acquired T cell mediated neuro-inflammatory disorder characterized by focal demyelination in the central nervous system (CNS) and axonal degeneration. Prevalence varies by region, but in the UK prevalence is between 100 and 300 per 100,000 people. The disease usually presents between the second and sixth decades of life and has a female to male ratio of 2:1. In most there is an episodic (relapsing-remitting) course, with focal neurological symptoms and signs developing over hours to days and improving across weeks to months. With time, the frequency of relapses decreases and there is a tendency to accrue progressive disability. In about 1 in 10 patients the disease is progressive with gradual accrual of disability from onset. Diagnosis is based on a clinical assessment, brain and spinal cord magnetic resonance imaging (MRI) and can be supported by cerebrospinal fluid analysis. There are a broad range of immunomodulatory treatments that reduce relapse rates (Table below), but developing treatments effective in preventing long-term disability remains a challenge.

Neurobiology of Demyelination and Axon Degeneration



CNS inflammation, demyelination and axonal degeneration are the pathological hallmarks of MS. Activation of autoreactive T cells to myelin-related antigens, transition through the blood brain barrier, activation of CNS B cells and microglial activation are important steps in these processes. The latter releases reactive oxygen species (ROS – Figure 2), which are significant mediators of cellular toxicity. Oligodendrocytes are injured in the inflammatory milieu resulting in demyelination. Axonal injury occurs early on and progresses over time, disrupting action potential propagation and axon transport. Current therapies target these processes, reducing inflammatory activity with therapeutic effect.

Figure 1: MRI scan of a MS brain
T2 weighted axial view of MRI brain scan from a patient with relapsing remitting MS. Multiple white matter T2 hyperintense lesions in orientation and distribution typical for MS.

Figure 2: Important ROS reactions
a – Generation of superoxide anion from molecular oxygen by NADPH-oxidase (nicotinamide adenine dinucleotide phosphate) as part of respiratory burst. **b** – Generation of nitric oxide by action of nitric oxide synthases (NOS), in particular inducible NOS as part of the respiratory burst. **c** – Detoxification of superoxide anion to oxygen and water through actions of superoxide dismutases (SODs) and peroxidases e.g. catalase.

Genes and the Environment

Ever since the first descriptions of MS by Charcot in 1865, clinicians and scientists have considered the risk factors for developing MS. There is evidence of a polygenetic determinant of risk, in particular specific human leukocyte antigen haplotypes confer higher susceptibility. In addition, environmental factors such as exposure to infectious agents may modify this risk.

Epidemiological studies confirm variation in the incidence of MS within and between countries and a latitudinal gradient with higher risk further from the equator. Latitude alone however fails to explain intra-regional differences, which may be better explained by ethnicity-related susceptibility and migration patterns. There is for example a lower incidence of MS in Americans with African ancestry compared with those of North European ancestry[1].

Twin studies[2] confirm a genetic determinant of risk, which is polygenetic. In keeping with an autoimmune basis to disease, HLA haplotypes, in particular DR2, have been identified as susceptibility factors.

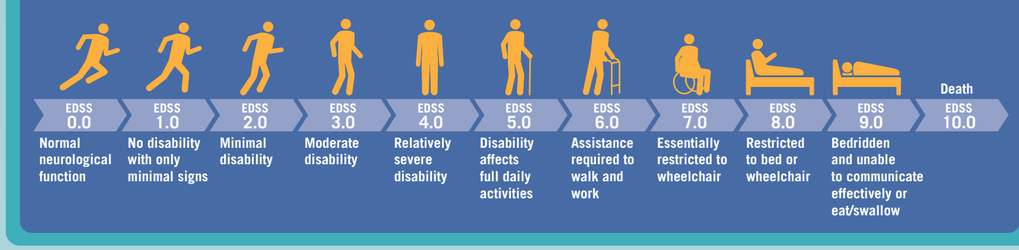
Epidemiological studies show an association between specific viral infections and MS risk. Epstein Barr virus exposure during an age-linked period of susceptibility is an emerging hypothesis as an environmental risk factor for MS. In addition, low vitamin D levels are linked to risk of relapse, and studies are assessing whether vitamin D replacement influences MS disease course.

Measuring Disease Activity and Disability

Central to our understanding of an inflammatory basis for MS relapses is the concept of disease activity. MR imaging in its capacity to demonstrate subclinical CNS inflammation is a powerful tool in the measurement of disease activity (Figure 1). Loss of CNS volume (atrophy), calculated between interval scans, also correlates with the gradual accrual of disability in progressive disease.

Measuring disability is essential to assessing potential treatment effects on progressive disease. The Expanded Disability Status Scale (EDSS) although initially described in 1961[3], remains the *de facto* standard in clinical trials as a measure of disability. As a primarily motor system dependent scale with non-linear ordinal characteristics, EDSS is an insensitive measure of change in disability. The Multiple Sclerosis Functional Composite (MSFC) was developed to improve on this and generates a parametric, continuous variable. MSFC improves on EDSS by formally assessing cognition, and being more sensitive to change. Other potential surrogates for disability such as optic coherence tomography, are being researched.

The Expanded Disability Status Scale (EDSS)



Drug Targets

There are many licensed drug treatments for relapsing-remitting Multiple Sclerosis, which reduce the burden of relapse. Interferon β-1b was the first of these, introduced in 1993 and is of modest efficacy. More effective agents often with a more significant adverse event profile have been developed, in particular the monoclonal antibodies. Oral agents of modest efficacy and good tolerability such as dimethyl fumarate and teriflunomide, have further expanded our formularies.

Despite good progress there remains no significant randomized control trial evidence, showing that any of these therapies have significant impact on long-term disability.

Drug	Target	Effect
Interferon β	Interferon receptor and STAT signaling pathways	Pleiotropic – modulates various aspects of immune system
Glatiramer acetate	Possibly MHC II on antigen presenting cells	Hypothesized induction and activation of suppressor T cell population
Teriflunomide	Inhibitor of mitochondrial dioorate dehydrogenase	Reduces uridine synthesis Impairs clonal expansion of activated lymphocytes
Dimethyl fumarate[4]	Kelch-like ECH-associated protein 1	Activates Nrf2 antioxidant response pathway
Natalizumab[5]	α4 integrin receptor	Impairs migration of activated autoreactive T cells into CNS
Alemtuzumab[6]	CD52	Peripheral B and T cell depletion Modulates autoreactive immune response

Products available from Tocris

α4β1 Integrins
BIO 1211, BIO 5192, LDV FITC
ASIC1
Amiloride, Psalmotoxin 1
ASK1
MSC 2032964A, TC ASK 10
Ca^{2+}-Activated Potassium Channels
Apamin, CyPPA, 1-EBIO, NS 309, TRAM 34, UCL 1684
Cannabinoid Receptors
ACEA, Arvanil, GP 1a, JWH 133, (*R*)-(+)-Methanandamide, WIN 55,212-2
Chemokine Receptors
BMS CCR2 22, BX 471, BX 513, J 113863, RS 102895, RS 504393
Complement
Compstatin, NDT 9513727, PMX 205, PMX 53, W 54011
Cytokines
AS 101, CRID3, 4-IPP, Pirfenidone, SC 144, Thalidomide
IFNγ
Andrographolide, Resiquimod
Immunosuppressants
Azathioprine, Cyclosporin A, FK 506 Mycophenolic acid, Rapamycin, Teriflunomide, Triptolide
Inward Rectifier Potassium (K_{ir}) Channels
Gambogic acid, ML 133
Interleukin-2 Inducible T cell Kinase (ITK)
BMS 509744, CTA 056, PF 06465469
Glutamate (Ionotropic) Receptors
Lamotrigine isethionate, Riluzole
Na^+/Ca^{2+} Exchanger
Benzamil, Bepridil, KB-R7943, SN-6, YM 244769
Neural Stem Cells
17-AAG, INDY, Neuropathiazol, ProINDY, SU 5402
Neuronal Metabolism
Etifoxine, Methylprednisolone, MOG (35-55), Myelin Basic Protein (87-99), Nogo-66 (1-40), PLP (139-151)
Nrf2
DMF, CDDO Im, Curcumin
ROS
SIN-1, SNAP, Spermine NONOate, Tempol
RXR Agonists
Bexarotene, Docosahexaenoic acid, Fenretinide, HX 630, Isotretinoin, Retinoic acid
Sphingosine-1-phosphate Receptors
CS 2100, CYM 5442, SEW 2871, Sphingosine-1-phosphate, VPC 23019, W146
STAT3
Colivelin, NSC 74859, Stattic
Tankyrase
JW 55, MN 64, XAV 939
TRPM4
9-Phenanthrol, DIDS
Vitamin D
Calcitriol, EB 1089
Voltage-Gated Potassium Channels
4-Aminopyridine, ADWX 1, CP 339818, Kaliotoxin, Margatoxin
Voltage-Gated Sodium Channels
APETx2, Flecainide acetate, Lidocaine, QX 314 chloride, Tetrodotoxin citrate, Veratridine
Wnt Inhibitors
Cardionogen 1, FH 535, IWP 2, IWP 4, Wnt-C59

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